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Arteriohepatic Dysplasia: A 16-Year Follow-up During Treatment With Cholestyramine

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THIS REPORT PRESENTS 16 years of a clinical history of a patient with liver abnormalities. Although partial intrahepatic biliary atresia was the first diagnosis, this was corrected to arteriohepatic dysplasia following publication recently of an article by Riely and associates.[1] The prolonged history of the disease, liver biopsy studies over 15 years, cholestyramine therapy for 16 years and the finding of anatomic features new to this syndrome warrant this case report.

Report of a Case

The patient, a woman now 19 years old, was first seen by the author in 1965 when she was 3. Symptoms then were continual diarrhea, pruritus and elevated temperatures. Both parents are American Jews of Ashkenazi background; a single female half-sibling is normal. Pregnancy was uneventful. Birth was full term with a weight of 3 kg (6 lb, 10 oz). Neonatal jaundice was recorded, with a bilirubin of 6 mg per dl that by 3 weeks of age was 1.8 mg per dl. Pruritus was first noted at 3 weeks. By 8 weeks of age, a heart murmur and bulky stools were described and intermittent heterotropia was noted soon thereafter. Developmental landmarks were normal; the infant sat at 7 months and walked and began to use single words at 15 months.

On physical examination in 1965 the child was noted to be irritable and had excoriations over her body. Weight was 14 kg (31 lb), height 95 cm (37 in). A pulmonic systolic murmur was heard. Liver and spleen were not felt and the rest of the physical examination showed no abnormalities. Laboratory findings (Table 1) suggested cholestasis. She was admitted to hospital for study. Gallbladder series and intravenous cholangiogram gave normal findings, as did a biopsy of the small bowel. Liver biopsy showed "intrahepatic ductal atresia" (Figure 1).

Among the laboratory test results obtained at that time were a 24-hour fecal fat of 37 grams (average less than 6 grams per 24 hours), a serum calcium of 9.8 mg per dl, and a serum bile acid of 4.4 mg per dl. Following that hospital stay a serum protein-bound iodine of 6.8 μg per dl was obtained.

While in hospital, a cardiac consultant diag-

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TABLE 1.—*Selected Laboratory Test Results Over 16 Years*

	Liver Function Tests				*Treatment*		
Date	*Cholesterol mg/dl*	*Bilirubin mg/dl*	*SGOT Units/ml*	*Alkaline Phosphatase Units/ml*	*Cholestyramine*	*Phenobarbital*	*Prednisone*
1963 (born)	..	6.0	..	..			
1963 (3 mos)	..	1.5	..	..			
1965	360	2.2	120	30*			
1967-1968	..	1.6	225	60*			
1970	260	..	100	120*			
1976	263	..	159	1,350†			
1978	..	..	106	1,060†			
1979, Feb	254	0.6	94	620†		15 mg q.i.d.	
1979, May	..	..	83	547†			40 mg
1979, Jun	..	..	..	137†			
1979, Jul	296	..	81	165†			
1979, Oct	299	..	64	283†			15 mg
1979, Nov	320	..	76	160†			
1980	..	..	..	..			
1981	255	0.7	84	242†			

*King-Armstrong Units.
†International Units.

nosed pulmonic stenosis. A final diagnosis of partial intrahepatic atresia was made. Cholestyramine one teaspoon three times daily was prescribed, with replacement of fat-soluble vitamins in the form of standard cod liver oil capsules twice daily and vitamin K. This relieved the pruritus and further fever did not occur. The diarrhea lessened.

Several events of note followed over the intervening years. Severe dental caries were evident by age 5. Surgical operation for heterotropia was required by age 10, at which time an erythrotoxin was also noted. Headache and apparent papilledema led to a neurology consultation with a resultant diagnosis of pseudotumor cerebri at age 11. This condition subsided without treatment. Repeat symptoms of cystitis led to a urologic consultation at age 13, at which time intravenous pyelography was done, showing reduplicated ureters and renal pelves (Figure 2). Menses occurred normally by age 14.

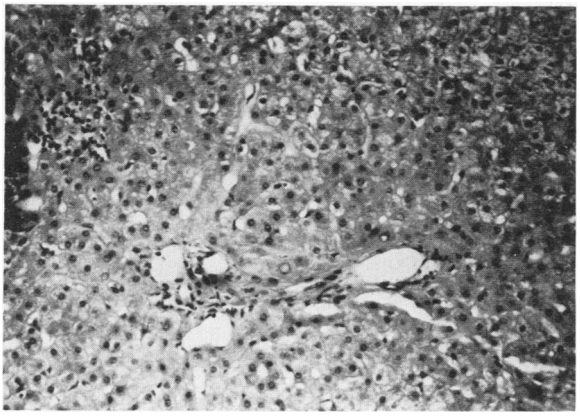

Figure 1.—Microphotograph from percutaneous liver biopsy, 1965, age 3 years, portal triad. The portal vein is easily recognized. Structures suggesting bile ducts can be seen but are not definitely identified. Focal mononuclear infiltrate is noted. (Reduced from magnification ×100.)

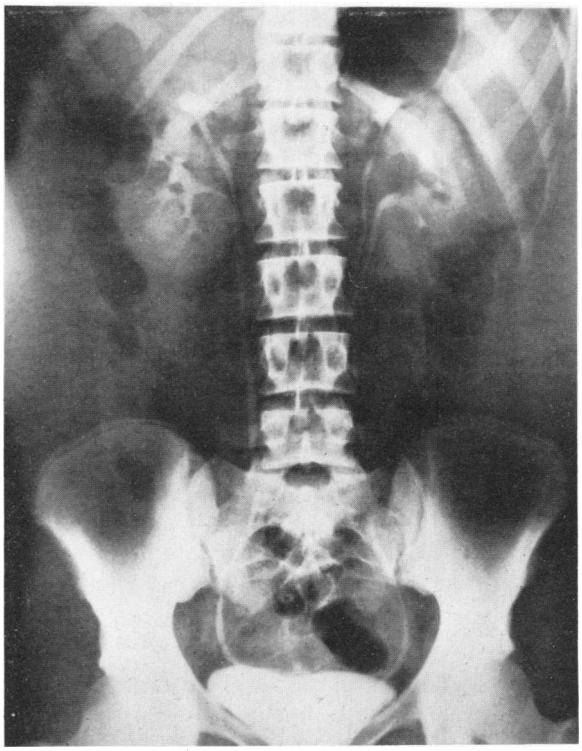

Figure 2.—Intravenous pyelography film showing reduplicated renal pelves and ureters.

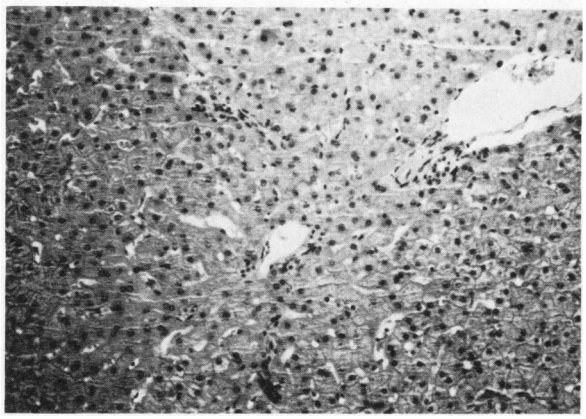

Figure 3.—Microphotograph from percutaneous liver biopsy, 1979, age 17 years, portal triad. A normal bile duct is seen (reduced from magnification ×100).

Efforts to withdraw cholestyramine led to recurrent pruritus whenever attempted. At age 16 a liver biopsy was again done and this time the biopsy specimen was normal (Figure 3). A gallbladder study likewise gave normal findings (Figure 4). A roentgenogram of the chest did not show abnormalities in heart contour (Figure 5). A three-month course of phenobarbital, 15 mg four times daily, and a five-month course of prednisone at a slowly declining dosage from an initial dose of 40 mg daily were instituted. Liver function tests remained abnormal, although the alkaline phosphatase showed substantial improvement (Table 1). Phenobarbital and prednisone were then discontinued. In late 1980 administration of cholestyramine was also discontinued, this time without recurrence of the pruritus.

The patient graduated from high school without difficulty. She engages in normal activities including a full range of physical pursuits. She appears normal, although of small stature like the rest of her family. Her facies appear normal (a photograph was declined). The murmur persists unchanged, but she has no signs of heart impairment.

Key laboratory tests are noted in Table 1. Par-

ticular attention is directed to the persistent abnormality of the serum glutamic oxaloacetic transaminase (SGOT, also known as serum aspartate aminotransferase) and serum cholesterol. An improving trend is seen for the serum alkaline phosphatase.

Discussion

This case report adds additional findings to the syndrome first described by Watson and Miller in 1973[2] and later by Alagille and co-workers in 1975.[3] Watson and Miller described the cases of 26 children from five families. Of the 26 children, 5 seemed normal, 11 had liver involvement, 14 had cardiac abnormalities, and 9 had both liver and heart abnormalities. Following jaundice at birth, liver disease tended to be mild, although pruritus sometimes persisted and the liver function tests sometimes remained abnormal. Hepatomegaly was not a regular feature and liver biopsy often gave normal findings. One case was reported in which the patient lived to age 20. Skeletal abnormalities, a characteristic facies and a bifid renal pelvis were described as associated features. Watson and Miller cited a probable similar case described by Vermassen and Buddaert in 1962. Watson and Miller concluded that they were describing a new syndrome that was familial, with predominant cardiac and hepatic features, of variable penetrance, and with occasional associated skeletal and renal features. The entity was generally rather benign.

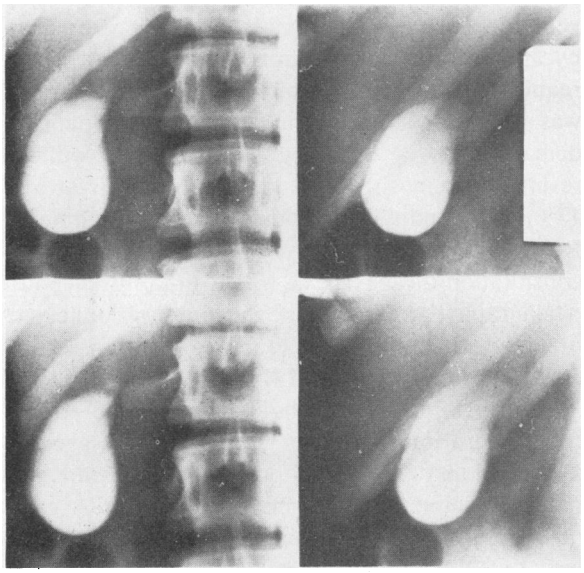

Figure 4.—Film of normal oral cholecystogram, 1978.

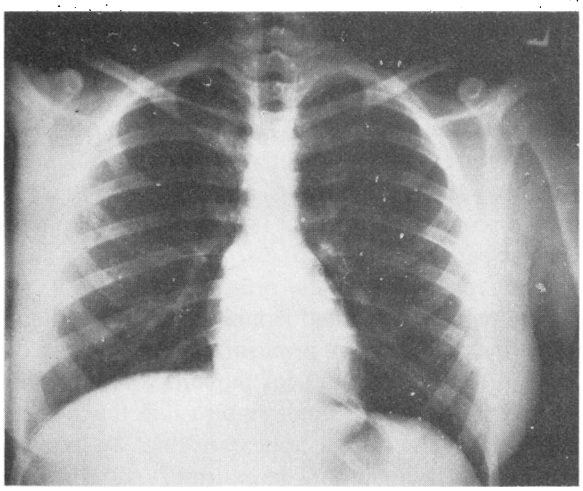

Figure 5.—Film of normal roentgenogram of the chest, 1978.

Alagille's group[3] apparently independently described the same entity in 1975. Earlier reports from this group in 1969[4] and again in 1970[5] did not focus separately on the subgroup with heart murmurs, skeletal abnormalities and the more benign clinical outcome. Other authors reporting the same syndrome include Greenwood and co-workers[6] in 1976 and Henricksen and colleagues[7] in 1977.

Arteriohepatic dysplasia is distinct from the forms of congenital cholestasis described in 1951 by Ahrens and associates[8] and grouped under the heading of atresia or dysplasia of the intrahepatic bile ducts. Ahrens' series and similar subsequent ones refer to a serious progressive disease with jaundice, xanthomas and death.

Special attention should be given to Lottsfeldt and co-workers'[9] case report; J. B. Carey, Jr., a coauthor, here extended the use of his cholestyramine from its application in primary biliary cirrhosis to intrahepatic atresia.

Summary

The case reported here adds the following information to the entity of arteriohepatic dysplasia: (1) A 13-year interval between two liver biopsies is available, with no morphologic liver abnormality found. (2) Reduplicated ureters are described for the first time in this entity. (3) Serum liver function tests gave persistently abnormal findings, including hypercholesterolemia. (4) A 15-year period of continuous use of cholestyramine, supplemented with fat-soluble vitamin replacement, appeared to have no effect on liver, bone, teeth or sexual maturation. (5) It was possible to dis-

continue therapy with cholestyramine after many years of administration.

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Refer to: Shragg TA, Albertson TE, Fisher CJ Jr: Cyanide poisoning after bitter almond ingestion. West J Med 136:65-69, Jan 1982

Cyanide Poisoning After Bitter Almond Ingestion

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ACUTE CYANIDE POISONING occurs relatively infrequently.[1] With the increasing use of amygdalin (commonly known as Laetrile) and other cyanogenic glycosides for alternative cancer therapy, accidental cyanide poisoning may become more common. Because of its rapid onset and the highly lethal nature of cyanide, many patients die before getting medical care.[1] Unfortunately, even when patients do obtain medical care the correct diagnosis is often delayed until well into their hospital course.[2,3] In reporting a case of cyanide poisoning, Graham and colleagues[2] noted the paucity of cases in which cyanide blood levels had been reported. They further questioned the efficacy and safety of the traditional therapy of intravenous sodium nitrite and sodium thiosulfate. We have recently treated a severe case of cyanide poisoning in which cyanide blood levels and the response to therapy were well documented.

ABBREVIATIONS USED IN TEXT

$A\text{-}aO_2$ = alveolar-arterial difference in oxygen
CVP = central venous pressure
FIO_2 = fraction of inspired oxygen
PCWP = pulmonary capillary wedge pressure
$\dot{Q}s/\dot{Q}t$ = right-to-left intrapulmonary shunt
SEM = standard error of the mean
$T_{1/2}$ = cyanide half-life in blood

Report of a Case

A 67-year-old woman weighing 60 kg (132 lb) was diagnosed as having carcinoma of the large bowel a year before the hospital admission described in this report. The tumor was judged to be resectable, but the patient refused either surgical therapy or consideration of chemotherapy. Eight months before admission to hospital, for a two-month period she self-administered injectable Laetrile purchased in Mexico. Subsequently, because of the expense of the injectable form, the patient switched to Laetrile tablets. The tablets were taken erratically but probably on an average of every other day over the next six months. Two weeks before the onset of her present illness, the patient was given a bag of bitter almonds by a friend, allegedly to help increase her "protein intake" and also for "medicinal purposes." Initially she ground up four to five bitter almonds and mixed them with water. Approximately 30 to 45 minutes after ingestion of the mixture, she became light-headed, and had nausea and vomiting with crampy abdominal pains. The symptoms subsided over the course of the evening and she felt well the next morning. On the night of admission she again made a slurry of water with 12 bitter almonds. She experienced a severe bout of crampy abdominal pain within 15 minutes after ingestion. The patient went into her bathroom and collapsed. Her daughter quickly called for an ambulance and en route to the hospital, a blood sample was taken and naloxone hydrochloride and 50 percent dextrose solution were administered, but failed to produce a response.

On arrival in the emergency room, the patient

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